## REMARKS

Claims 26-45 are pending in the application.

35 U.S.C. § 112, First Paragraph Rejection

The Examiner has indicated that claims 27, 30-42, and 44-45 contain "subject matter which was not descried in the specification in such a way as to enable one skilled in the art...to make and/or use the invention." More particularly, the Examiner has indicated that claim 27 is drawn a method of employing an antibody recognition site having the following properties: (i) the antibody is specific for oxidation specific epitopes present in the core of atherosclerotic plaques; and (ii) the antibody is specific for oxidized low density lipoprotein and malondialdehyde low density lipoprotein.

*Antibody specificity*

The Examiner questioned how a single antibody can be specific for both oxidized low-density lipoprotein (OxLDL) and malodialdehyde low-density lipoprotein (MDA-LDL). Applicants submit that atherosclerotic plaques are complex mixtures of a number of proteins, lipids, necrotic cells and other factors. In such a mixture, one would find both OxLDL and MDA-LDL distributed in different patterns. Both MDA-LDL and OxLDL contain multiple epitopes, some of which they share in common.

LDL is a complex mixture of proteins, lipids and cholesterol. Antibodies do not recognize antigens as large as LDL, which is a very large complex of thousands of different molecules, including a large protein, apoB (MW 500 kDa), and cholesterol, cholesterol esters, triglycerides and phospholipids (combined MW 2 X $10^6$ kDa). Instead antibodies recognize small epitopes (i.e. discrete portions) of antigenic molecules or particles. Protein epitopes are typically 8 to 12 amino acids in length (molecular weight about 9 to 13 kDa) as this is the size peptide that is presented in the major histocompatability complex (MHC) on the surface of an antigen presenting cell. More complex antigens, including combinations of lipids and proteins such as those present in OxLDL and MDA-LDL can be recognized, but the epitope recognized by the antibody is only a small portion of the complex molecule. Both OxLDL and MDA-LDL are derived from the same particle, LDL. It is therefore not surprising that the components of the modified particles share eptitopes. Monoclonal

antibodies are known that bind to both OxLDL and MDA-LDL, such as the IK17 antibodies described in the subject specification. The Applicants submit that one would readily be able to test for antibodies with similar specificities. The IK17 antibody was found by a phage panning method which is well known to those skilled in the art and taught in the specification (see page 9-10 of the specification). Antibodies can be selected for binding to a first antigen, either OxLDL or MDA-LDL, and then selected against the other antigen. Antibodies selected can then be tested for binding to atherosclerotic plaques. One skilled in the art would readily be able to determine if the antibody bound to the core of the atherosclerotic plaque. Alternatively, other assays, such as competition assays, can be performed to determine if antibodies have overlapping epitopes and specificities. Such assays are well known to those skilled in the art.

*Sequences identified in SEQ ID. NO.: 1 and 2*

The sequences given in SEQ ID NO.: 1 and 2 are **not** the sequences of the oligonucleotides used to amplify the variable antibody regions as suggested by the Examiner in the Office Action. The sequences are from the antibody identified after amplification of the library by PCR and the panning for and isolation of phage that bound to the antigen as described in the specification on page 10, lines 19-24. The antibody defined by the variable chain sequences binds to the core of the atherosclerotic plaque as well as binding OxLDL and MDA-LDL. Therefore, Applicants were in possession of the claimed antibodies, and submit that claim 27 is fully supported by the specification.

As the remaining claims are directed towards the use of the antibody of claim 27 in methods well known to those skilled in the art, such as the detection methods of claim 35, or in methods enabled by the specification, such as the identification of plaques used in treatment, are all enabled by the specification. Therefore, the rejection of claims 27, 30-42, and 44-45 under 35 U.S.C. § 112, first paragraph, is traversed.

Double Patenting

The Examiner has rejected claims 27 and 35 for double patenting over claims 1-7 of U.S. Patent No. 6,375,925 (the '925 patent). The Examiner has also rejected claim 31 and 32 over claims 1-7 of the '925 patent further in view of Tsimiksa et al., 1999. Applicants respectfully request

reconsideration of this ground for rejection. As previously discussed and agreed to by the Examiner, the '925 patent is limited to antibodies that are specific for a single epitope. The specification stresses the importance of specificity to a **single** epitope, thus teaching away from selecting an antibody that **cross reacts** with two different epitopes. As discussed in the subject specification, "all of the antibodies previously described were monospecific, binding to only one form of OxLDL" (col. 1, paragraph [0010].) The Examiner reasons that "the claims read on fragments thereof or small molecule analogs which do not require cross reactivity of two or more epitopes." This conclusion is incorrect. The claims recited that the binding agent is "specific for oxidation specific epitopes found on copper-induced oxidized low density lipoprotein (Cu-OxLDL) **and** malondialdehyde low density lipoprotein (MDA-LDL)" (claim 27, emphasis added.) Thus, the claims present an **absolute requirement for cross reactivity.** For this reason, Applicants respectfully request withdrawal of this ground for rejection.

Rejection Under 35 U.S.C. §102(e)

The Examiner has indicated that claims 27, 31 and 34-35 are unpatentable under 35 U.S.C. §102(e) over Witztum et al., U.S. Patent No. 6,225,070 ('070.) More particularly, the Examiner reasons that the mouse monoclonal antibodies, E06, E013, E014 and E017, anticipate the recited claims. Applicant respectfully disagrees.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. MPEP 2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). First, the monoclonal antibodies that are claimed and described in the '070 patent are mouse, not human antibodies. Second, the antibodies described in the '070 patent bind to different antigens than IK17. Further, as mentioned previously, the subject claims are directed towards highly specific and cross reacting antibodies. This selection for antibodies that bind to an epitope that two different forms of OxLDL share is not taught or suggested in the '070 patent.

In further support of the Examiner's rejection of Applicants' previously filed Amendment, the Examiner incorrectly reasons that the '070 patent anticipates the claims, because both the antibodies described in the '070 patent and the antibodies described in the instant specification are used "to monitor atherosclerotic plaques". However, this is merely the **use** of the claimed

antibodies, and does not serve to anticipate the claimed antibodies having a different **structure/function** relationship with the atherosclerotic plaques. Additionally, the Examiner draws the technical conclusion that since the antibodies described in the '070 patent inhibit uptake by macrophages, the antibodies claimed in the instant application must also. Applicants cannot determine why the Examiner has **deemed inherent** to the antibodies of the present invention that they inhibit uptake as well.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 30-32, 36 and 38-42 under 35 U.S.C. §103(a) over the '070 patent in view of Tsimikas et al, 1999. As discussed above, the antibodies of the instant invention are clearly distinguished from the EO antibodies of the '070 patent. As the methods taught in claims 30-32, 36 and 38-42 are directed to the use of the antibodies of the instant invention they cannot be obvious in view of the prior art. Therefore, the rejection of the claims under 35 U.S.C. §103(a) is traversed.

The Examiner rejected claim 36 under 35 U.S.C. §103(a) over the '070 patent in view of Fuster el al. As discussed above, the antibodies of the instant invention are clearly distinguished from the EO antibodies of the '070 patent. As the method taught in claims 36 is directed to the use of the antibodies of the instant invention they cannot be obvious in view of the prior art. Therefore, the rejection of the claim under 35 U.S.C. §103(a) is traversed.

The Examiner rejected claim 36 under 35 U.S.C. §103(a) over the '070 patent in view of Tsimikas et al, (WO 98/21581). As discussed above, the antibodies of the instant invention are clearly distinguished from the EO antibodies of the '070 patent. As the methods taught in claim 36 is directed to the use of the antibodies of the instant invention they cannot be obvious in view of the prior art. Therefore, the rejection of the claim under 35 U.S.C. §103(a) is traversed.

The Examiner rejected claims 33, 34, 37 and 44-45 under 35 U.S.C. §103(a) over the '070 patent in view of Tsimikas et al, (WO 98/21581). As discussed above, the antibodies of the instant invention are clearly distinguished from the EO antibodies of the '070 patent. As the methods taught in claims 33, 34, 37 and 44-45 are directed to the use of the antibodies of the instant invention they cannot be obvious in view of the prior art. Therefore, the rejection of the claims under 35 U.S.C.

§103(a) is again traversed.

As previously discussed, the '070 patent does not teach or suggest every limitation of claim 27, which is the only independent claim in the instant application. As amended herein, claim 27 recites an antibody with a combination of **four distinct structural characteristics**, and this combination is absent from the '070 patent. Since Tsimikas is merely a more extensive characterization of one of the antibodies that is already well characterized in the '070 patent, it goes no further toward rendering claim 27 obvious than the '070 patent would alone. It is a well settled principle that if an independent claim is found to be novel and nonobvious over the prior art, the more narrow dependent claims must necessarily also be found to be novel and nonobvious over the same prior art.

Moreover, the '070 patent fails to suggest that one should select an antibody with the four recited structural characteristics of claim 27, and Tsimikas does not supply what is missing from the '070 patent. Since obviousness cannot be found absent such a suggestion, this combination of references fails to render the present claims obvious.

Claims 33, 34, 37 and 44-45 are also alleged to be unpatentable under 35 U.S.C. §103(a) over the '070 patent in view of PCT WO 98/21581 ('581.) More particularly, the Examiner indicates that the '070 patent does not teach administration of an antigen to reduce residual label, but that the '581 application teaches such a method. The Examiner concludes that, on this basis, the recited claims are obvious over the '070 patent in further view of the '581 application. However, just like Tsimikas, the '581 application is merely a further characterization of the MDA2 and NA59 antibodies that are already described in the '070 patent. Accordingly, this combination of references also fails to teach or suggest an antibody having the same combined characteristics as those recited in independent claim 27. For this reason, the recited claims cannot be obvious over this combination of references.

The Examiner has not provided any basis for rejecting Applicants' previously presented arguments, except to say they were "not found persuasive". Accordingly, Applicants respectfully request the Examiner to furnish reasoning, not just a mere conclusion, as to why the prior art references in combination render the claims obvious, when not all of the limitations of the instant claims are either taught or suggested by the prior art, either alone or in combination.

## SUMMARY

If the Examiner believes that it would facilitate prosecution, Applicants' Attorney, Laura M. Lloyd may be contacted at (619) 230-7714 or at llloyd@gordonrees.com.

Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 50-1990 and please credit any excess fees to such deposit account.

Respectfully submitted,

Dated: 9-5-07

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